University of New England - Maine
Access Provided by:
SILVERCHAIR

Chapter 18: Adrenal Gland Disorders

INTRODUCTION

- Hyperfunction of the adrenal glands leads to excess production of cortisol (*Cushing syndrome*) or aldosterone (*hyperaldosteronism*).
- Adrenal gland hypofunction includes primary adrenal insufficiency (*Addison disease*) or secondary insufficiency.

CUSHING SYNDROME: CLINICAL PRESENTATION

- The most common findings in Cushing syndrome are central obesity and facial rounding (90% of patients). Peripheral obesity occurs in 50%. Dorsocervical fat accumulation (buffalo hump) is nonspecific, but supraclavicular fat pads are more specific for Cushing syndrome. Patients are often described as having moon faces and a buffalo hump.
- Other findings may include myopathy or muscular weakness, abdominal striae, hypertension, glucose intolerance, psychiatric changes, gonadal dysfunction, facial plethora (reddish complexion), and amenorrhea and hirsutism in women.
- Up to 60% of patients develop Cushing-induced osteoporosis, 40% present with back pain, and 20% progress to spinal compression fractures.

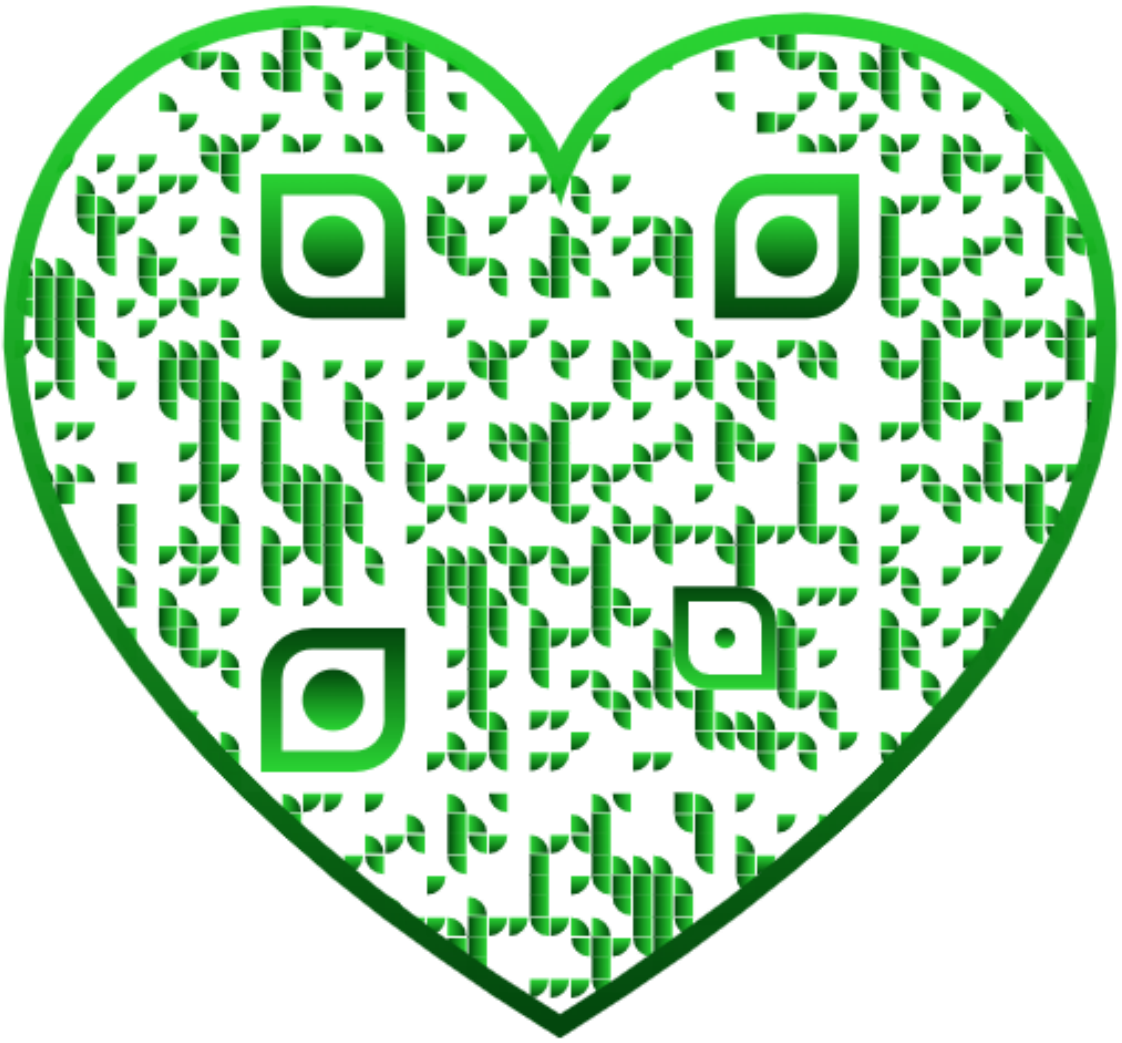
CUSHING SYNDROME: DIAGNOSIS

- Hypercortisolism can be diagnosed using one or more of the following: 24-hour urinary free cortisol (UFC), midnight plasma cortisol, late-night (11 PM) salivary cortisol, and/or low-dose dexamethasone suppression test (DST).
- Tests to determine etiology include plasma adrenocorticotropic hormone (ACTH); adrenal vein catheterization; metyrapone stimulation test; adrenal, chest, or abdominal computed tomography (CT); corticotropin-releasing hormone (CRH) stimulation test; inferior petrosal sinus sampling; jugular venous or cavernous sinus sampling; and pituitary magnetic resonance imaging (MRI).
- Adrenal nodules and masses are detected via high-resolution CT or MRI.

CUSHING SYNDROME: TREATMENT

- Goals of Treatment: Reduce morbidity and mortality, restore normal function by eliminating the source of hypercortisolism, and minimize pituitary or adrenal deficiencies.
- Treatment plans for Cushing syndrome based on etiology are included in **Table 18-1**.

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility



University of New England - Maine
Access Provided by:
SILVERCHAIR INFORMATION/SYSTEMS

TABLE 18-1

Treatment Options for Cushing Syndrome Based on Etiology

Etiology	Nondrug	Generic Drug Name	Dosing		
			Initial Dose	Usual Range	Maximum
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone	0.5–1 g/day, divided every 4–6 hours	1–2 g/day, divided every 4–6 hours	6 g/day
		Ketoconazole	200 mg once or twice a day	200–1200 mg/day, divided twice daily	1600 mg/day
Pituitary dependent	Surgery, irradiation	Mitotane	0.5–1 g/day, increased by 0.5–1 g/day every 1–4 weeks	1–4 g daily, with food to decrease GI effects	12 g/day
		Metyrapone	See above	See above	See above
		Mifepristone	300 mg once daily, increased by 300 mg/day every 2–4 weeks	600–1200 mg/day	1200 mg/day or 20 mg/kg/day
		Cabergoline	0.5 mg once weekly	0.5–7 mg once weekly	7 mg/week
		Osilodrostat	2 mg twice daily	2–7 mg twice daily	60 mg/day
		Pasireotide	0.6–0.9 mg twice daily	0.3–0.9 mg twice daily	1.8 mg/day
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole	See above	See above	See above
Adrenal carcinoma	Surgery	Mitotane	See above	See above	See above

ACTH, adrenocorticotropic hormone; GI, gastrointestinal.

NONPHARMACOLOGIC THERAPY

- Surgical resection of the tumor is the preferred treatment for both ACTH-dependent and ACTH-independent Cushing syndrome.
- Transsphenoidal resection of the pituitary tumor is the first-line treatment for Cushing disease. Radiotherapy, used for tumors invading the dura or cavernous sinus, improves symptoms in ~50% of patients within 3–5 years but increases the risk for hypopituitarism.
- Laparoscopic adrenalectomy is preferred for unilateral adrenal adenomas or when pituitary surgery or radiotherapy fails or is not feasible.

PHARMACOLOGIC THERAPY

- Pharmacotherapy is typically second-line treatment in patients ineligible for surgery and may also be used preoperatively or as adjunctive therapy in postoperative therapy (**Table 18-1**). Monotherapy is rarely used palliatively when surgery is not an option.

Steroidogenesis Inhibitors

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

- **Metyrapone** inhibits 11 β-hydroxylase, inhibiting cortisol synthesis, causing sudden decrease in cortisol concentration. This drop triggers a compensatory rise in plasma ACTH. With cortisol synthesis blocked, adrenal steroidogenesis shifts toward androgen production, causing side effects like acne and hirsutism. Aldosterone inhibition may lead to natriuresis and blood pressure changes. Nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, and allergic rash may occur often indicating overtreatment.

- **Ketoconazole** inhibits cytochrome P-450 enzymes, including 11 β-hydroxylase and 17 α-hydroxylase, effectively lowering serum cortisol levels after several weeks. It also has antiandrogenic activity, which may be beneficial in women but can cause gynecomastia and hypogonadism in men. Common side effects include reversible elevation of hepatic transaminases, gastrointestinal (GI) discomfort, and dermatologic reactions. Due to hepatotoxicity risk, monitor liver function tests at baseline and weekly serum alanine aminotransferase (ALT) throughout therapy. Ketoconazole may be combined with metyrapone for synergistic cortisol reduction, and its antiandrogenic effects may counteract metyrapone's androgenic activity.

- **Etomidate,** an imidazole derivative similar to ketoconazole, inhibits 11 β-hydroxylase and may have other mechanisms. Because it is only available in a parenteral formulation, its use is reserved for acute hypercortisolemia requiring emergency treatment or in preparation for surgery. Serum cortisol should be monitored frequently to prevent hypocortisolemia. Side effects include sedation, injection site pain, hypotension, myoclonus, nausea, and vomiting. The initial dose is 0.03 mg/kg IV bolus followed by a continuous infusion of 0.1–0.3 mg/kg/h.

- **Osilodrostat**, an oral 11β-hydroxylase, is used in patients with Cushing disease who are ineligible for or unresponsive to surgery. It is taken twice daily, with or without food. Correct hypokalemia and hypomagnesemia before use, and obtain ECG at baseline and 1 week after starting to monitor for QTc prolongation. Adverse effects include hypocortisolism, QTc prolongation, nausea, and headache.

Adrenolytic Agents

- **Mitotane** is a cytotoxic drug that inhibits the 11-hydroxylation of 11-deoxycortisol and 11-desoxycorticosterone in the adrenal cortex, reducing cortisol and corticosterone synthesis. Like ketoconazole, it takes weeks to months for full effect. Cortisol suppression is sustained in most patients and may persist after drug discontinuation in up to one-third. Mitotane causes degeneration of zona fasciculata and zona reticularis cells, leading to adrenal cortex atrophy; the zona glomerulosa is minimally affected during acute therapy but can be damaged with long-term use. Significant neurologic and GI side effects are common, warranting close monitoring or hospitalization at initiation. Nausea and diarrhea, typical at greater than 2 g/day, may be reduced by gradual dose titration and/or taking with food. CNS effects like lethargy and somnolence are also common. Reversible hypercholesterolemia and prolonged bleeding times can occur.

Neuromodulators of ACTH Release

- Pituitary secretion of ACTH is mediated by neurotransmitters such as serotonin, γ-aminobutyric acid (GABA), acetylcholine, and catecholamines. Although ACTH-secreting pituitary tumors (Cushing disease) partially self-regulate ACTH production, these neurotransmitters can still promote pituitary ACTH production. Consequently, drugs targeting these transmitters, including cyproheptadine, bromocriptine, cabergoline, valproic acid, octreotide, lanreotide, pasireotide, rosiglitazone, and tretinoin, have been proposed. Except for pasireotide, none have demonstrated consistent clinical efficacy for treating Cushing disease.

- **Cyproheptadine**, a nonselective serotonin receptor antagonist and anticholinergic drug, can decrease ACTH secretion in some patients with Cushing disease, but its use is limited by sedation and weight gain.

- **Pasireotide** (Signifor), a somatostatin analog, inhibits ACTH secretion by binding and activating somatostatin receptors, decreasing cortisol secretion. It is approved for the treatment of adults with Cushing disease for whom pituitary surgery is not possible or has failed. Side effects include nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, and QT prolongation.

Glucocorticoid-Receptor Blocking Agents

- **Mifepristone** (Korlym), a progesterone- and glucocorticoid-receptor antagonist, inhibits dexamethasone suppression and increases endogenous cortisol and ACTH levels in healthy individuals. It is effective in reversing hypercortisolism symptoms (hyperglycemia, hypertension, weight gain) and is FDA approved for endogenous Cushing syndrome in patients with type 2 diabetes or glucose intolerance who are ineligible for or unresponsive to surgery. Common adverse effects include fatigue, nausea, headache, arthralgia, peripheral edema, endometrial hyperplasia,

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

and hypokalemia.

CUSHING SYNDROME: EVALUATION OF THERAPEUTIC OUTCOMES

- Close monitoring of 24-hour UFC and serum cortisol is essential to identify adrenal insufficiency in patients with Cushing syndrome. Monitor steroid secretion with all drug therapy (except mifepristone) and give corticosteroid replacement if needed.

HYPERALDOSTERONISM: CLINICAL PRESENTATION

- Patients may complain of muscle weakness, fatigue, paresthesias, headache, polydipsia, and nocturnal polyuria.
- Signs may include hypertension, tetany/paralysis, and polydipsia/nocturnal polyuria.
- A plasma aldosterone concentration-to-plasma renin activity (PAC-to-PRA) ratio or aldosterone-to-renin ratio (ARR) >30 ng/dL per ng/(mL·h) (830 pmol/L per mcg/(L·h) and a PAC >15 ng/dL (420 pmol/L) is suggestive of primary hyperaldosteronism (PA).
- Other laboratory findings include suppressed renin activity, elevated plasma aldosterone, hypernatremia (>142 mEq/L), hypokalemia, hypomagnesemia, elevated serum bicarbonate (>31 mEq/L), and glucose intolerance.

HYPERALDOSTERONISM: DIAGNOSIS

- Initial diagnosis is made by screening patients with suspected PA. Any patient with a blood pressure >150/100 mm Hg measured on three separate days and with treatment-resistant hypertension should be screened. Others at risk include those with diuretic-induced hypokalemia; hypertension and adrenal incidentaloma; hypertension and sleep apnea; hypertension and a family history of early onset hypertension or cerebrovascular accident at an age <40 years and those with hypertension and a first-degree relative diagnosed with PA.
- Screening for PA is most often done using the PAC-to-PRA ratio (also known as the ARR). An elevated ARR is highly suggestive of PA.
- If the ARR is positive, confirmatory tests to exclude false-positives include the oral sodium-loading test, saline infusion test, fludrocortisone suppression test (FST), and captopril challenge test. A positive test indicates autonomous aldosterone secretion under inhibitory pressures and is diagnostic for PA.

HYPERALDOSTERONISM: TREATMENT

NONPHARMACOLOGIC THERAPY

- Aldosterone-producing adenomas are treated by laparoscopic resection of the tumor, curing up to 72% of patients. If surgery is contraindicated, medical management with an aldosterone receptor antagonist is often effective.

PHARMACOLOGIC THERAPY

- Aldosterone-receptor antagonists are the treatment of choice for bilateral adrenal hyperplasia.

  ✓ **Spironolactone** (Aldactone), a nonselective aldosterone receptor antagonist, competes with aldosterone for binding at aldosterone receptors and prevents negative effects of aldosterone receptor activation. The initial dose is 25 mg daily titrated upward every 4–8 weeks. Most patients respond to doses between 25 and 400 mg/day given in single or divided doses. Adverse effects include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia.

  ✓ **Eplerenone** (Inspra), a selective aldosterone receptor antagonist, has high affinity for aldosterone receptors and low affinity for androgen and progesterone receptors, causing fewer sex-steroid–dependent effects than spironolactone. Dosing starts at 50 mg daily, with titration every 4–8 weeks to 50 mg twice a day; some patients may require 200–300 mg/day.

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

✓ **Amiloride** (Amiloride), a potassium-sparing diuretic, is less effective than spironolactone, and patients often require additional therapy to adequately control blood pressure. The initial dose is 5 mg twice daily, with a usual range of 20 mg/day given in two divided doses; doses up to 30 mg/day may be necessary.

✓ Second-line options include calcium channel blockers, ACE inhibitors, and diuretics such as chlorthalidone, although none have PA-specific outcome data.

- Treatment of secondary aldosteronism depends on cause. Resolving extra-adrenal aldosterone stimulation usually corrects the disorder. Spironolactone is used until the etiology is identified.

ADRENAL INSUFFICIENCY: CLINICAL PRESENTATION

- Patients with adrenal insufficiency commonly complain of weakness, weight loss, GI symptoms, salt craving, headaches, memory impairment, depression, and postural dizziness.
- Early symptoms of acute adrenal insufficiency also include myalgias, malaise, and anorexia. As the situation progresses, vomiting, fever, hypotension, and shock develop.
- Signs of adrenal insufficiency include increased skin pigmentation, postural hypotension, fever, decreased body hair, vitiligo, amenorrhea, and cold intolerance.

ADRENAL INSUFFICIENCY: DIAGNOSIS

- The short cosyntropin stimulation test is used to assess patients with suspected hypercortisolism. An increase to a cortisol level of ≥18 mcg/dL (500 nmol/L) rules out adrenal insufficiency.
- Patients with Addison disease have an abnormal response to the short cosyntropin stimulation test. Plasma ACTH levels are usually elevated (400–2000 pg/mL or 88–440 pmol/L) in primary insufficiency versus normal to low (5–50 pg/mL or 1.1–11 pmol/L]) in secondary insufficiency. A normal cosyntropin-stimulation test does not rule out secondary adrenal insufficiency.
- Other tests include the insulin hypoglycemia test, the metyrapone test, and the CRH stimulation test.

ADRENAL INSUFFICIENCY: TREATMENT

- Goals of Treatment: Limit morbidity and mortality, return the patient to a normal functional state, and prevent episodes of acute adrenal insufficiency.

NONPHARMACOLOGIC THERAPY

- Inform patients of treatment complications, expected outcomes, proper medication administration and adherence, and possible side effects.

PHARMACOLOGIC THERAPY

Corticosteroids

- The preferred agents are **hydrocortisone** and **cortisone acetate,** usually administered twice daily, with the goal of establishing the lowest effective dose while mimicking the normal diurnal adrenal rhythm. Once-daily **prednisolone** is an alternative when adherence is a concern.
- Recommended starting doses are hydrocortisone 15–25 mg daily, approximately equivalent to cortisone acetate 20–35 mg daily or prednisolone 3–5 mg daily (**Table 18-2**). For hydrocortisone or cortisone, two-thirds is given in the morning and one-third is given 6–8 hours later.
- Monitor the patient's symptoms every 6–8 weeks to assess proper glucocorticoid replacement. Measure body weight, postural blood pressures, subjective energy levels, and signs of glucocorticoid excess.

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

- In primary adrenal insufficiency, **fludrocortisone acetate** 0.05–0.2 mg orally once daily replaces mineralocorticoid loss and maintains volume. For parenteral use, 2–5 mg of **deoxycorticosterone trimethylacetate** in oil is administered intramuscularly every 3–4 weeks. Mineralocorticoid replacement attenuates hyperkalemia, and salt restriction is not needed during fludrocortisone therapy. Some cases may not require mineralocorticoid therapy, as glucocorticoids (especially in large doses) also bind to mineralocorticoid receptors.
- Most adrenal crises result from glucocorticoid dose reductions or lack of stress-related dose adjustments. Patients receiving corticosteroid replacement therapy should add 5–10 mg hydrocortisone (or equivalent) to their normal daily regimen shortly before strenuous activities, such as exercise. During severe physical stress (eg, febrile illness, injury), they should double their daily dose until recovery.
- Treatment of secondary adrenal insufficiency is similar to primary disease, except that mineralocorticoid replacement is usually unnecessary.

TABLE 18-2

Relative Potencies of Glucocorticoids

Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-Retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100–300	0
Dexamethasone	30	0.75	100–300	0

PHARMACOLOGIC THERAPY OF ACUTE ADRENAL INSUFFICIENCY

- Acute adrenal insufficiency (adrenal crisis or Addisonian crisis) is a true endocrine emergency. Major clinical features include volume depletion and hypotension that resolve within 1–2 hours after parenteral glucocorticoid administration.
- Stressful situations, surgery, infection, and trauma can increase adrenal requirements, especially those with underlying adrenal or pituitary insufficiency.
- The most common cause of adrenal crisis is HPA-axis suppression brought on by abrupt withdrawal of chronic glucocorticoid use.
- **Parenteral hydrocortisone** is preferred for its glucocorticoid and mineralocorticoid activity. Start with 100 mg IV rapid infusion, followed by 200 mg over 24 hours as a continuous infusion or a 50-mg intermittent bolus every 6 hours. Continue IV administration for an additional day at a reduced dose of 100 mg over 24 hours. If it is stable at that time, switch to oral hydrocortisone 50 mg every 6–8 hours, followed by a taper to the individual's chronic replacement needs.
- **Fluid replacement** is often needed. Use IV dextrose 5% in normal saline solution at a rate to support blood pressure.

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility

- For hypoglycemia, infuse 25% dextrose in water 2–4 mL/kg (maximum single dose of 25-g dextrose).
- If hyperkalemia persists after hydrocortisone maintenance, add additional mineralocorticoid supplementation with **fludrocortisone acetate** 0.1 mg daily.
- Patients with adrenal insufficiency should carry a card or wear a bracelet or necklace that contains information about their condition. They should also have easy access to injectable hydrocortisone or glucocorticoid suppositories for emergencies or during times of physical stress, such as fever or injury.

ADRENAL INSUFFICIENCY: EVALUATION OF THERAPEUTIC OUTCOMES

- The endpoint of therapy for adrenal insufficiency is difficult to assess in most patients, but a reduction in excess pigmentation is a good clinical marker. Development of features of Cushing syndrome indicates excessive replacement.

See Chapter e101, Adrenal Gland Disorders, authored by Angelina Vascimini, Steven M. Smith, and John G. Gums, for a more detailed discussion of this topic.

Downloaded 2026-3-8 5:18 PM Your IP is 176.123.19.29
Chapter 18: Adrenal Gland Disorders,
©2026 McGraw Hill. All Rights Reserved. Terms of Use • Privacy Policy • Notice • Accessibility